REMARKS

Claims 1-50 are pending in the application. Claims 23-50 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention. Claims 1-22 have been rejected.

Claims 1, 17, and 18 have been amended. Support for the amendments can be found throughout the specification as originally filed. No new matter has been added by the proposed amendments. New claims 51-54 have been added to specifically claim individual members of the Markush group recited in claims 1 and 18. Amendment of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to more particularly point out and distinctly claim the invention to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Amendments to the Specification

Applicants have amended page 82 of the specification and submit herewith a revised sequence listing including the sequences of both KIAA 18 and KIAA 96 as SEQ ID NO. 10 and SEQ ID NO. 11, respectively. In addition, Applicants also submit herewith a Statement from the Applicants' representative stating that the amendatory material consists of the same material incorporated by reference in the application as originally filed.

Claim Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-17 are rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement. In particular, the Office Action asserts that given the broad scope of the claims in an art that is unpredictable, it would require undue experimentation for one skilled in the art to perform the method of the claimed invention. Applicants respectfully traverse this rejection in light of the amendments and remarks below.

To expedite prosecution of the application, Applicants have amended the claims to more specifically define the invention. Amended claims 1, 17 and 18 specifically recite the sequences of KIAA 18 and KIAA 96, SEQ ID NO. 10 and SEQ ID NO. 11, respectively.

In light of the ample teachings of the Applicants' Specification, including the use of an art-recognized cell line model for prostate cancer, and the amendments to the claims, Applicants respectfully request that the Examiner withdraw the enablement rejection.

Applicants direct the Examiner to the teaching of the Applicants' Specification in which the application states that the KIAA 18 and KIAA 96 genes were initially identified using Affymetrix Genechip™ technology as being *statistically, differentially expressed* ($p<0.05$) in diseased tissues when compared to normal tissue. (*See* for example, Specification page 9, lines 32-34). Expression of the prostate specific antigen (PSA) gene, which has been extensively studied as a biomarker in prostate cancer and has proven to be predictive of clinical responses in prostate cancer patients to therapy, was used as an internal control in the experiments disclosed in the application (*See* page 10, lines 6-9 of the Specification). For example, Example 1 demonstrates that the over-expression pattern of KIAA 18 in response to androgen was similar to that of PSA (*See* page 80, line 29-34 of the Specification).

Moreover, Applicants point out that LNCaP is a well-characterized cell line that has been widely used in the study of prostate cancer for over 20 years. The enclosed seminal journal article establishes the LNCaP cell line from a metastatic lesion of human prostatic adenocarcinoma and shows that the malignant properties, hormonal responsiveness and drug sensitivity of the prostate adenocarcinoma are maintained (Horoszewicz, J.S. "LNCaP Model of Human Prostatic Carcinoma" *Cancer Research*, 43, 1809-1818 (1983)). The growth and maintenance of prostate cancer cells are often dependent on androgen (*See* Background). The androgen-responsive feature of LNCaP makes it a useful *in vitro* model for the study of regulation of prostate related genes since the expression of many prostate-specific proteins require functionally differentiated, androgen-responsive cells. Those skilled in the art view LNCaP cells as an established *in vitro* model of prostate cancer as evidenced by the fact that this seminal article establishing the LNCaP cell line has been cited over 800 times in other peer-reviewed journals (See enclosed record of citation). These references show that, at the time the

application was filed, the skilled artisan appreciated the existence of a correlation between the LNCaP cell line and prostate cancer.

Applicants further provide working examples in the Specification that bear a correlation to the scope of the invention. Well-characterized human cancer cell lines, such as LNCaP, are routinely used and have proven to be highly predictive of *in vivo* results. This correlation of the *in vitro* cell line model to *in vivo* results was validated in the Specification (see Example 4). In Example 4, RNA that was isolated from normal prostate glands (control) and prostate tumors with different Gleason grades were analyzed. KIAA 18 expression increased as the tumor grade increased while KIAA 96 expression decreased as the tumor grade increased. According to MPEP 2164.02, "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating." (See also, *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995), reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).

Applicants submit herewith a Declaration of Dr. Steven Haney pursuant to 37 C.F.R. §1.132 as further proof that the claimed methods were fully enabled by the Specification as filed. This Declaration establishes that one skilled in the art would recognize that the LNCaP cell line model used in the experiments described in the application is a well-characterized model of human prostate cancer and therefore, one would assume that since KIAA 18 expression was increased and and KIAA 96 expression was decreased in the LNCaP cell line model, expression of KIAA 18 and KIAA 96 would also be increased and decreased, respectively, in cancer tissue.

In light of the teachings in the Specification, the Declaration of Dr. Steven Haney pursuant to 37 C.F.R. §1.132, and amendments to the claims, Applicants respectfully request that the Examiner withdraw the enablement rejections.

Claim Rejection Under 35 U.S.C. § 103(a)

Claims 18-22 are rejected under 35 U.S.C. § 103(a) as being obvious over An *et al.* (U.S. 5,972,615) in view of Nagase *et al.* (*DNA Res.*, Vol. 2, pages 37-43, 1995). In particular, the Office Action asserts that An *et al.* teach a method of detecting metastatic prostate disease in a subject comprising detecting in a subject sample at a first point in time the expression of prostate

specific-transglutaminase (see column 4, line 16-25) and comparing the level of expression with that of a control. Applicants respectfully traverse this rejection. The Examiner is respectfully requested to withdraw the anticipatory rejection in light of the claim amendments and following remarks.

Claim 18, and dependent claims thereof, require the detection of "SEQ ID NO. 10 (KIAA 18) and SEQ ID NO. 11 (KIAA 96), or a combination thereof." for the monitoring of the progression of prostate cancer. An *et al.* teach that the specific transglutaminase, "prostate-specific transglutaminase" (GenBank Accession Nos. L34840, I20492), cytokeratin 15 (GenBank Accession No. X07696), or semenogelin II (GenBank Accession Nos M81652 and M81651) or combinations thereof, can be used in diagnosing prostate cancer (See Col. 73, lines 28-39 and TABLE 4 of An *et al.*). An *et al.* does not teach or suggest the use or even the existence of any "KIAA" markers, let alone the specific markers, SEQ ID NO: 10 (KIAA 18) and SEQ ID NO 11 (KIAA 96), that are recited in the amended claims, as admitted by the Examiner in the Office Action.

The deficiencies of An *et al.* are not remedied by Nagase *et al.* The Examiner asserts that it would have been obvious to a person of ordinary skill in the art to modify the method "for detecting the expression of KIAA markers as taught by An et al." with the teachings of KIAA 96 as taught by Nagase *et al.* since "Nagase *et al.* taught the role of KIAA 96 in signal transduction and similarities with protein kinase gene family." While Nagase *et al.* disclose the coding sequences of 40 genes including KIAA 96, Nagase *et al.* do not teach or suggest using KIAA 96 as a marker for monitoring prostate cancer. Nagase *et al.* simply note that the KIAA 96 gene carried sequences with similarities to the genes of the protein kinase family. Neither Nagase *et al.* nor An *et al.* teach that protein kinases can be used as *markers* for prostate cancer in humans.

In order to satisfy the burden of obviousness in light of combination, the Examiner must show some objective teachings leading to the combination. The invention should not be employed as a blueprint to simply pick and choose elements from different sources to defeat patentability. An *et al.* do not teach or suggest that any KIAA marker is associated with prostate cancer. Furthermore, Nagase *et al.* do not associate KIAA 96, a protein kinase, with prostate

cancer. Therefore, there is no motivation for one skilled in the art to combine teachings of An *et al.* with that of Nagase *et al.*

For all the reasons recited above, it is clear that neither the An *et al.* reference nor the Nagase *et al.* reference discloses or suggests the methods of the present invention, that there is no motivation to combine these references, and that even if combined they do not disclose or suggest the method of the present invention. Thus, these references fail to disclose or suggest every element recited by independent claim 18. Because every limitation of an independent claim is imported to dependent claims, claims 19-22 are also allowable. Applicants, therefore, respectfully request that the Examiner withdraw all rejections.

Claim Rejection Under 35 U.S.C. § 112 First Paragraph

Claims 1-22 have been rejected over the use of the abbreviated term KIAA. In response, the claims have been amended to further define the specific KIAA markers, KIAA 18 and KIAA 96, as SEQ ID No. 10 and SEQ ID No. 11, respectively. The Examiner is respectfully requested to withdraw this rejection in light of the amendments.

CONCLUSION

In summary, the above-identified patent application has been amended and reconsideration is respectfully requested for all the reasons set forth above. In the event that the amendments and remarks are not deemed to overcome the grounds for rejection, the Examiner is kindly requested to telephone the undersigned representative to discuss any remaining issues.

Respectfully submitted,

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